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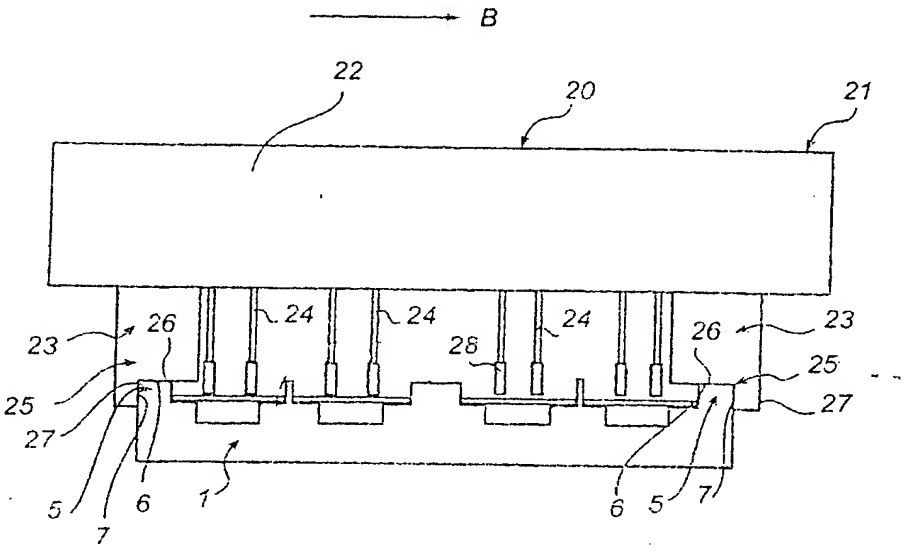
(54) Title: SYSTEM AND METHOD FOR PROCESSING TISSUE SECTION SAMPLES



(57) Abstract: The invention concerns a system for handling and processing tissue section samples and a method for processing tissue sections using the system according to the invention. Thus the system according to the invention comprises a tray for carrying microscopic slides at predetermined positions on the tray. The tray is connectable to an aspirating device for sliding engagement therewith and thereby co-ordinating nozzle positions of said device with the positions of the microscopic slides. According to the method of the invention a multiple number of samples may be prepared and placed on treatment surfaces, such as on microscopic slides. Liquid is added to the samples. The samples are positioned at a predetermined distance below the aspirating nozzles and solution is aspirated from the samples. The samples are positioned below the nozzles with a sliding horizontal motion.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

System and method for processing tissue section samples.

The present invention relates to histochemistry, including immunohistochemistry. The invention concerns a system for handling and processing tissue section samples and a method for processing tissue sections using the system according to the invention. The invention also concerns a tray for handling and incubating tissue sections on microscopic slides.

Histochemistry is a branch of biochemistry devoted to the study of the chemical composition and structure of human, animal and plant tissues. One of the methods used for studying tissues is microscopy. To obtain contrast between individual cells and other tissue components, the tissue sections are normally stained before the microscopic examination. In immunohistochemistry labelled antibodies and other ligands including nucleic acid probes are used for directly viewing of the cellular and tissue distribution of a molecule.

Most of these staining methods involve a large number of incubations for various time periods, separated by washing steps to remove reagents in excess. For a long time all operations were carried out by hand. This procedure involved adding and removing reagent solutions to each tissue section sample with a pipette, washing the samples by immersing the slides in a large buffer volume and changing the buffer a couple of times and finally wiping around the tissue sections by hand using a paper tissue before incubating with the next reagent solution. This sequence is then repeated for several steps of the procedure. For hospital- and research laboratories handling large amounts of tissue samples, this tedious staining procedure limited the amount of samples that could be examined every day. In accordance to this manual procedure one person can process about 15 tissue sections a day. Some years ago, manufacturers started to develop equipment for automated staining of tissue sections on

microscopic slides and a number of different types are now on the market, one of which is "Cadenza" from Shandon Scientific (U.K.). In the Cadenza system tissue sections are stained on a vertically standing slide.

However, these automated staining equipments have not solved all the problems. For example, the Cadenza has the disadvantages that only one reagent can be applied per slide and that a limited number of slides can be stained each day, namely a maximum of 20 slides a day. Tissue sections on different areas of the slide may sometimes be stained differently resulting in unevenly stained preparations. Furthermore, it is not possible to work in the presence of detergents, as is the case when using intracellular stains.

US-4 274 359 discloses a biological slide staining apparatus comprising a tray having predetermined positions for slides. The tray is arranged for horisontal insertion in the apparatus for staining of the slides. Removal of liquid from the slides is performed by blowing air onto the slides and by tilting of the slides. With this method of removing liquid from the slides, the liquid will be spread over a major part of the slide surface.

WO 99/44031 discloses a slide staining apparatus having slides mounted on a rotary horisontal carousel. Rinse liquids are removed by an aspiration head having a flattened bottom with eight holes. For removal of liquid the aspiration head is lowered vertically down into a cavity formed by a slide frame, surrounding the staining surface. The aspiration head is within this cavity moved into contact with the liquid covering the surface, so as to spread the liquid over the surface and create a capillary gap during aspiration of liquid. In WO 99/44031 it is also pointed out that this aspirator head ensures an accurate removal of liquid. For removal of liquid from consecutive samples it is necessary to:

a) rotate the carousel,

b) lower the aspirator head into the cavity,

c) aspirate, and

d) rise the aspirator head.

A mutual problem with the prior art devices is that it is not possible to process more than one reagent sample on each slide.

An object of the present invention is to overcome problems related to previous staining methods by providing a new and improved system and method for processing tissue section samples for use in the staining procedure.

A specific object of the invention is to provide for a higher efficiency in the wash procedure in the staining process related to microscopic examination of tissue samples.

Another specific object of the invention is to provide an apparatus and a method for staining tissue samples, wherein the staining of different tissue samples and with different reagents on the same surface, e.g. a slide surface, is enabled, thus enabling a higher efficiency.

These objects, as well as other objects that will be apparent from the description below, have now been obtained according to the present invention by providing a system and a method for processing tissue section samples according to claim 1 and 9.

The objects are also achieved by a tray according to claim 8.

Thus the system according to the invention comprises a tray for carrying microscopic slides at predetermined positions on the tray. The tray is connectable to an aspirating device for sliding engagement therewith and thereby co-ordinating nozzle positions of said device with the positions of the microscopic slides.

According to the method of the invention a multiple number of samples may be prepared and placed on treatment

surfaces, such as on microscopic slides. Liquid is added to the samples. The samples are positioned at a predetermined distance below the aspirating nozzles and solution is aspirated from the samples. The samples are positioned below the nozzles with a sliding horizontal motion.

In accordance with the invention the tray is capable of carrying a number of tissue samples at the same time. Thus a greater number of tissue samples can be prepared in advance and thereafter be processed parallelly, which leads to drastically altered efficiency.

Thanks to the inventive way of removing liquid solution from the tissue samples by aspiration of the solution, a high reproducability and a very precise and fast removing of the liquid is accomplished. As will be explained below, by aspiration, physical phenomena related to the surface tension of the solution can be used to reach very accurate results.

By connecting a plurality of nozzles with a plurality of samples and permitting a relative displacement by a sliding longitudinal motion, a high number of consecutive samples can be treated efficiently in consecutive steps. Also, the distance between nozzles and samples can be controlled and kept fixed in a simple fashion, thus rendering the aspirating step even more precise and efficient. The relative sliding motions has also proven to be an efficient way of positioning a plurality of samples at predetermined locations below a number of nozzles such that consecutive liquid removals from consecutive samples can be performed quickly.

The sliding horizontal motion is relative and could be performed with the tray or the aspiration device. High efficiency can with the method and system of the invention be reached either by placing a number of samples transversely for parallel liquid removal by a plurality of nozzles at the same time, or by placing a number of samples in a longitudinal row for liquid to be removed by a number of consecutive aspirating steps. By using both

directions, placing samples both transversely and longitudinally an even higher efficiency can be reached.

Thanks to the inventive way of removing liquid solution from tissue samples by aspiration with a plurality of nozzles and a sliding relative motion for co-ordinating the positions of the nozzles and positions of the slides, it has proven possible to process a plurality of samples on the same slide surface, without the need of walls between different samples. A specific reason therefore is that the liquid to be removed is in no way spread out horisontally but only aspirated upwards.

According to a preferred embodiment of the invention the treatment surfaces for the samples are microscopic slides or specific treatment surfaces on such slides.

According to a specifically preferred embodiment each tray has a first longitudinal guiding means for cooperation with a longitudinal guiding means on the aspirating device. By the longitudinal guiding means of the tray and the aspirating device respectively, the relative positions of the nozzles are controlled in a transverse direction and in a direction perpendicular to the tray.

The nozzles on the aspiration device are preferably arranged essentially equidistant to and perpendicular above the centre of samples on the microscopic slides placed on a tray, when liquid is aspirated. In a preferred embodiment of the invention the distance between samples, on slides at predetermined positions on the tray, and the tips of the nozzles on the aspirating device connected to the tray is 0,1-1,5 mm, preferably 0,3-1,0 mm, and most preferably 0,5-0,8 mm. The negative pressure used for the aspiration device is at least 1 mbar, preferably at least 20 mbar and most preferably at least 30 mbar and is less than 100 mbar, preferably less than 80 mbar and most preferably less than 50 mbar. A preferred range of the negative pressure is 30-50 mbar.

Preferably the system further comprises a dispensing device having a plurality of nozzles for dispensing small

accurate volumes of liquid solution to the tissue section samples. Thereby also the step of adding solution to samples is performed in a very efficient way, thus also rendering the staining process more efficient.

When the system comprises a dispensing device with a plurality of nozzles each tray preferably has a second longitudinal guiding means for co-operation with a longitudinal guiding means on the dispensing device. It should be noted that said first guiding means for the aspirating device and the second guiding means for the dispensing device might in specific embodiments be incorporated as one single guiding means.

The dispensing device is preferably stationary which gives the structure more stability when liquid is dispensed. In this embodiment the tray is moved to shift the relative positions between samples and nozzles.

The diameter of the tips of the nozzles on the dispensing device is 0,5-2,0 mm, preferably 0,5-0,8 mm, giving the dispensed water droplets a preferred size.

The slides are placed on the tray at predetermined positions. The slides can as mentioned above optionally be placed in a row in a longitudinal direction and/or in a transverse direction on the tray.

The tray may also be used for incubating the samples. According to one specific embodiment the tray has for this purpose a reservoir for water or the like to give the tissue samples a moist atmosphere during incubation and prevent them from drying. During incubation the tray may be provided with a removable closure to help creating a suitable incubation environment for the samples. It is of great advantage that the same tray can be used for washing and for incubation of the samples. Thereby a high efficiency in the processing of the samples can be achieved. Of specific importance for the efficiency is that each slide on the tray can form incubation vessels for a number of separate samples.

It is generally accepted that in order to obtain optimal results from a staining procedure, tissue sections must be washed efficiently, normally with a buffer solution, between the application of reagents. In a preferred embodiment of the present invention the liquid wash solution is dispensed by dispensing nozzles and aspirated with aspirating nozzles of the dispensing device and the aspirating device respectively. This accurate dispensation and aspiration of liquid leads to a reproducable wash resulting in high quality staining results of the tissue section samples. The physical relations behind the wash process is explained below.

According to one aspect of the invention the microscopic slides have got defined surfaces, preferably circular surfaces, for the tissue section samples and the defined surfaces are surrounded by a hydrophobic surface surface. Since the defined surfaces on each slide are surrounded by a hydrophobic surface, the surface tension can be used to retain a large volume of the wash solution on the defined surfaces.

When aspirating solution, the surface tension is used to aspirate a majority of the wash solution from the tissue section sample and its defined surface on the slide. When the majority of the wash solution is aspirated, the surface tension is finally used to retain a small amount of liquid on the tissue section sample. This small amount of liquid prevents the section from drying in between reagent treatments and helps spreading the reagent evenly across the surface of the tissue section leading to good staining results.

The invention will now be further described below with reference to the appended drawings showing a presently preferred embodiment.

Fig. 1a is a front view of an aspirating device and a tray connected to each other and forming part of a system for staining tissue samples.

Fig. 1b is a detail view of Fig. 1a.

Fig. 2 is a front view of a dispensing device and a tray connected to each other and forming part of a system for staining tissue samples.

Fig. 3 is a plan view of the tray according to Fig 1a.

Fig. 4 is a sectional view taken along line III-III in Fig. 3.

Fig. 5 is a plan view of a removable closure.

Fig. 6 is a sectional view taken along line VI-VI in Fig. 5.

Fig. 7 is a plan view of a microscopic slide forming part of a system for staining tissue samples.

Fig. 8 is a flow chart of a method for processing tissue section samples.

A presently preferred embodiment of a system for processing tissue section samples in accordance with the invention is illustrated in Figure 1a and b. The system comprises a tray 1 and an aspirating device 20 slidably connected with each other.

The aspirating device 20 comprises a body 21 formed by a transversely extending central beam 22 and two support legs 23 extending down from the beam 22. The beam 22 carries a number of aspirating nozzles 24 as will be explained below. The support legs 23 each has a guiding means 25 for co-operation with a corresponding first guiding means 5 on the tray 1.

The beam 22 comprises an eight-channel intake manifold with eight tubular nozzles 24 of stainless steel connected to one output tubing (not shown). The nozzles 24 are equipped with a plastic tubing 28 for easy adjustment of the length of the nozzles 24. The diameter of the tips of the nozzles 24 is in the range of 0,8-2,0 mm.

The guiding means 25 on the support legs 23 are longitudinal, i.e. directed perpendicularly to the drawing, and connectable to corresponding first longitudinal guiding means 5 on the tray 1. The guiding means 25 of the aspirating device 20 comprises downwards facing sides 26

and opposed inwards facing sides 27 co-operating slidingly with upper sides 6 and outwards facing sides 7, respectively on the tray 1. The downwards and upwards facing sides 26; 6 co-operate to control the vertical distance between the nozzle tips 29 and the tray 1. The outwards and inwards facing sides 7; 27 co-operate to decide the relative position between the tray 1 and the aspirating device 20 in a transverse direction B. The guiding means may of course be embodied alternatively, still providing co-operating longitudinal sliding areas that decide and preferably fix relative positions vertically and transversely between the aspirating device 20 and the tray 1. The guiding means 25 of the aspirating device 20 and the first guiding means 5 of the tray 1 are preferably made of acrylic plastic or might alternatively have another suitable low-friction material surface that enables a sliding movement between the tray 1 and the aspirating device 20.

The aspirating device 20 is when in use connected to a laboratory vacuum pump (not shown) capable of generating a vacuum in the range 1-100 mbar.

A stationary dispensing device 30, suitable for use with the system according to the invention is shown in Fig. 2. The dispensing device 30 is formed similarly to the aspirating device 20 and has a body 31 comprising a transversely extending central beam 32 and two support legs 33 extending down from the beam 32. The support legs 33 are in their lower ends connected by a bottom plate 40. The beam 32 carries a number of dispensing nozzles 34 as will be explained below. The support legs 33 and the bottom plate 40 together forms longitudinal guiding means 35 for co-operation with a corresponding second longitudinal guiding means 5a on the tray 1.

The dispensing device 30 has an eight-channel manifold with eight dispensing nozzles 34 of stainless steel. The diameter of the tip of the nozzles 34 is in the range 0,5-0,8 mm. The distance between the tips of the nozzles

34 on the dispensing device 30 and samples on slides 50 at predetermined positions on the tray 1, the tray 1 being connected to the dispensing device 30, is 5-20 mm.

The guiding means 35 of the dispensing device 30 is connectable to a corresponding second guiding means 5a on the tray 1 for a sliding movement of the tray 1 relative the stationary dispensing device 30. The second guiding means 5a of the tray 1 comprises the outwards facing sides 7 and the downwards facing side 8 of the tray 1. The guiding means 35 of the dispensing device 30 comprises opposed inwards facing sides 37 on the support legs 33 and an upwards facing side 41 on the bottom plate 40. In correspondence with the aspirating device 20, the guiding means 5b and 35 co-operate to decide the relative positions between the tray 1 and the dispensing nozzles 34.

The guiding means 35 on the dispensing device 30 and the second guiding means 5b on the tray 1 are made of acrylic plastic or another suitable material that makes a sliding movement possible.

The dispensing device 30 is connected to a glass syringe and a reservoir for liquid solution (not shown) for dispensing small accurate volumes of wash solution to samples placed on microscopic slides 50 on the tray.

The tray 1, illustrated in Figs. 3 and 4, is an elongated flat plate of acrylic plastic having an upper surface 10 four longitudinal grooves 11 and carrier surfaces 12 for microscopic slides. The grooves 11 start and end at a distance from the short sides of the tray 1. On the longitudinal sides of each groove 11 the carrier surfaces are provided in the form of flat elevations 12. The first and second guiding means 5 and 5b of the tray are as described above formed by elevated longitudinal sides 7, adjacent longitudinal upper surfaces 6 and a lower surface 8. The tray 1 has two thinner longitudinal partitions 13 and a thicker central partition in the form of a

longitudinal middle section 14 of the same height as the surrounding upper surface 10 of the tray.

Microscopic slides 50 are schematically shown in a left groove 11, and placed at predetermined positions on the tray 1 resting on the carrier surfaces 12. The slides 50 are placed with one of their short ends pointing in the longitudinal direction A of the tray 1. The tray can carry 12 slides 50, four slides 50 in the transverse direction B and three slides 50 in the longitudinal direction A.

The positions of the slides 50 are fixed in the transverse and longitudinal directions. The slides 50 are fixed in the transverse direction by one of the longitudinal inner walls 17 of the grooves 11.

The slides 50 on the tray 1 are fixed in a longitudinal direction between the end walls of the grooves 11.

The grooves 11 on the tray 1 comprises a central reservoir 19 that can be filled with water in order to give samples on the slides 50 a moist atmosphere during incubation. The tray 1 might also be equipped with a removable closure 60, see Figs. 5 and 6, which can be placed on the tray 1 during incubation. The removable closure 60 is slightly bigger than the tray 1 and is resting on the upper surface 10 of the tray 1 and in this way sealingly closes the tray 1. The removable closure 60 is a flat plate 61 of acrylic plastic with four border strips 62, 63, for keeping the closure 60 in place.

The tray may also be stackable and in this way be used as a lid for the tray below in a pile.

Now turning to fig 7, the microscopic slides 50 preferable used with the system of the invention are of standard size (75 x 25 mm) with 12 defined circular surfaces treatment 51 (two rows with six surfaces each), the surfaces 51 being surrounded by a hydrophobic stained surface 52. The treatment surfaces have a diameter of 8 mm. Slides 50 of this type are commercially available from ICN.

With reference to the flow chart of Fig. 8 a preferred method for processing tissue section samples will be described below.

In the first step, step 101, tissue section samples are positioned and fixed to the circular treatment surfaces on the microscopic slides 50, see fig 7. The tissues are first air dried on the circular surfaces on the slides and then fixed thereto with ice cold acetone in a cold cuvette. The samples are incubated on the slides at -20°C for 10 minutes. A circle is drawn around each circular surface with a wax pen to increase the hydrofobic barrier between the treatment surfaces.

The next step, step 102, entails adding water to the longitudinal grooves 11 on a tray 1 and positioning the slides 50 at predetermined positions on the carrier surfaces 12 on the tray 1.

Reference is now being made to fig 2 and 3. The tray 1 is connected to the stationary dispensing device 30, step 103, by inserting the tray 1 on top of the bottom plate 40 guided by the second guiding means 5a on the tray 1 and the guiding means 35 of the dispensing device 30.

Thereafter solution is added, step 104, to a first (along direction B) transverse row (not shown) of circular treatment surfaces formed by a first transverse row of microscopic slides 50 on the tray 1. Liquid is dispensed with a glass syringe (not shown) into the manifold of the dispensing device 30 and equal amounts of liquid are pressed out of each nozzle 34 onto the circular surfaces on the slides 50. Normally 100 µl of liquid wash solution is used for each circular surface.

If more samples shall be processed, step 105, the tray 1 thereafter is moved with a sliding movement, step 106, in a longitudinal direction A so that the second transverse row of treatment surfaces 51 on the slides 50 are positioned below the nozzles 34 and solution is thereafter dispensed, step 104, to the surfaces 51.

If there are further samples to be processed, step 105, the tray 1 is moved again, step 106, and solution is dispensed to the new row of circular surfaces, step 104, and so on until all the surfaces 51 on the slides 50 on the tray 1 are processed, step 105.

The samples are thereafter often incubated, step 107, on the tray 1 for twenty minutes at room temperature. During the incubation the tray 1 is sealed by a removable closure 60, see fig 5, and the water in the grooves 11 of the tray causes a moist atmosphere and prevents the samples from drying.

Turning now to fig 1a and 1b the aspirating device 20 is connected to the tray 1, step 108. The aspirating device 20 and the tray 1 are connected by the guiding means 25 on the aspirating device 20 and the guiding means 5 on the tray 1. This can be done optionally when the tray is still connected to the dispensing device 30. The aspirating device 20 is then moved to the first transverse row of treatment surfaces 51 formed by the first transverse row of microscopic slides 50 on the tray 1 with a substantially horisontal sliding movement in a longitudinal direction.

The solution is then aspirated from the treatment surfaces, step 109, with the aspirating device 2 connected to a vacuum pump. The negative pressure used is preferably 50 mbar or lower. The solution is removed almost instantaneously leaving only a small amount of liquid on the tissue section samples. This remaining liquid is retained by the surface tension. The distance between the nozzles 24 of the aspiration device 20 and the tissue section samples is in the range 0,5-0,8 mm during the aspiration.

If more samples shall be processed, step 110, the aspirating device 20 is thereafter moved with a sliding movement, step 111, in a longitudinal direction (see fig 3) along the tray 1 so that the second row of treatment surfaces on the slides 50 are positioned under the noz-

zles 24 and solution is thereafter aspirated, step 109, from the treatment surfaces.

If further samples need to be processed, step 110, the aspirating device 20 is moved again, step 111, and solution is aspirated from the new row of circular surfaces, step 109, and so on until all the surfaces on the slides on the tray 1 are processed.

A staining reagent can now be added to the tissue section samples with a separate standard multiwell pipette. The positions of the surfaces on the slides are adapted after the distance between the tips on the multiwell pipette. Normally a volume of 50 µl of reagent solution is added to each circular surface. The samples are incubated on the tray 1. During the incubation the tray is sealed by a removable closure and the water in the grooves 11 of the tray 1 gives a moist atmosphere and prevents the tissue section samples from drying. After incubating the samples the reagent is aspirated with the aspirating device 20 and a wash procedure according to the above described steps 104-111 is started by adding liquid wash solution to the samples with the dispensing device 30. The wash procedure is performed three times between each reagent treatment.

CLAIMS

1. A system for processing a plurality of tissue section samples comprising:

at least one tray (1) for carrying at least one slide (50) at a predetermined position on said tray (1);

an aspirating device (20) with a plurality of nozzles (24) and means for supplying negative pressure;

each tray (1) having guiding means (35) for co-operation with corresponding guiding means (25) on the aspirating device (20), the guiding means being connectable for sliding movement in a longitudinal direction (A) and for co-ordinating the position of the nozzles (24) with the positions for the microscopic slides (50) on the tray (1).

2. A system according to claim 1, wherein the guiding means (5) of each tray (1) comprises a first longitudinal guiding means (6) and the guiding means of the aspirating device (20) comprises a corresponding longitudinal guiding means for co-operation with said first guiding means (5).

3. A system according to claim 1 or 2, further comprising a dispensing device (30) with a plurality of nozzles (34) and means for dispensing small accurate volumes of liquid.

4. A system according to claim 3, wherein each tray (1) has a second longitudinal guiding means (7) for co-operation with a corresponding guiding means (37) on the dispensing device (30), said second guiding means (7) and guiding means of the dispensing device (37) movement in a longitudinal direction (A) and for co-ordinating the position of the nozzles (34) with the positions of the microscopic slides (50) on the tray (1).

5. A system according to any of the claims 1-4, wherein the nozzles (24) of the aspirating device (20) are arranged in a transverse direction at predetermined distances from the guiding (26) means of the aspiration

device (20) and, when the device (20) is connected to the tray (1), at a predetermined height perpendicular above the tray (1).

6. A system according to any of the claims 1-5, further comprising microscopic slides (50) on the tray (1), the slides (50) having defined surfaces (51) for samples.

7. A system according to claim 6, wherein the defined surfaces (51) are surrounded by a hydrophobic surface (52).

8. A tray (1) for handling and incubating tissue section samples on microscopic slides (50) comprising: an essentially elongated plate having predetermined positions for the microscopic slides (50) and at least one longitudinal groove (11), the tray (1) having longitudinal guiding (6) means for co-operation with corresponding guiding means (26) on an aspirating device (20), the guiding means being connectable for sliding movement in a longitudinal direction (A) and for co-ordinating the position of nozzles (24) on the aspiration (20) device with the positions for the microscopic slides (50) on the tray (1).

9. Method for processing a plurality of tissue section samples comprising the steps of:
a) positioning and fixation of the samples to at least one treatment surface;
b) adding a liquid solution to the samples;
c) fixing the samples in a plane at a predetermined distance below aspirating nozzles (24);
d) positioning the samples in predetermined positions below the aspirating nozzles (24) by a relative sliding motion in a substantially horizontal direction; and
e) aspirating solution from the samples.

10. Method according claim 9, wherein the step of positioning and fixation of the samples to at least one treatment surface entails positioning and fixation of samples to microscopic slides (50) and positioning the slides (50) at predetermined positions on a tray (1).

11. Method according to claim 9 or 10, wherein the distance between the samples on the treatment surfaces (50) and the aspirating nozzles is 0,1-1,5 mm, preferably 0,3-1,0 mm and most preferably 0,5-0,8 mm.

12. Method according to claim 10, wherein the microscopic slides (50) have defined surfaces (51) for samples, the surfaces (51) being surrounded by a hydrophobic surface (52).

13. Method according to any of the claims 9-12, wherein the negative pressure used for the aspiration of liquid solution is at least 1 mbar, preferably at least 20 mbar and most preferably at least 30 mbar and is less than 100 mbar, preferably less than 80 mbar and most preferably less than 50 mbar.

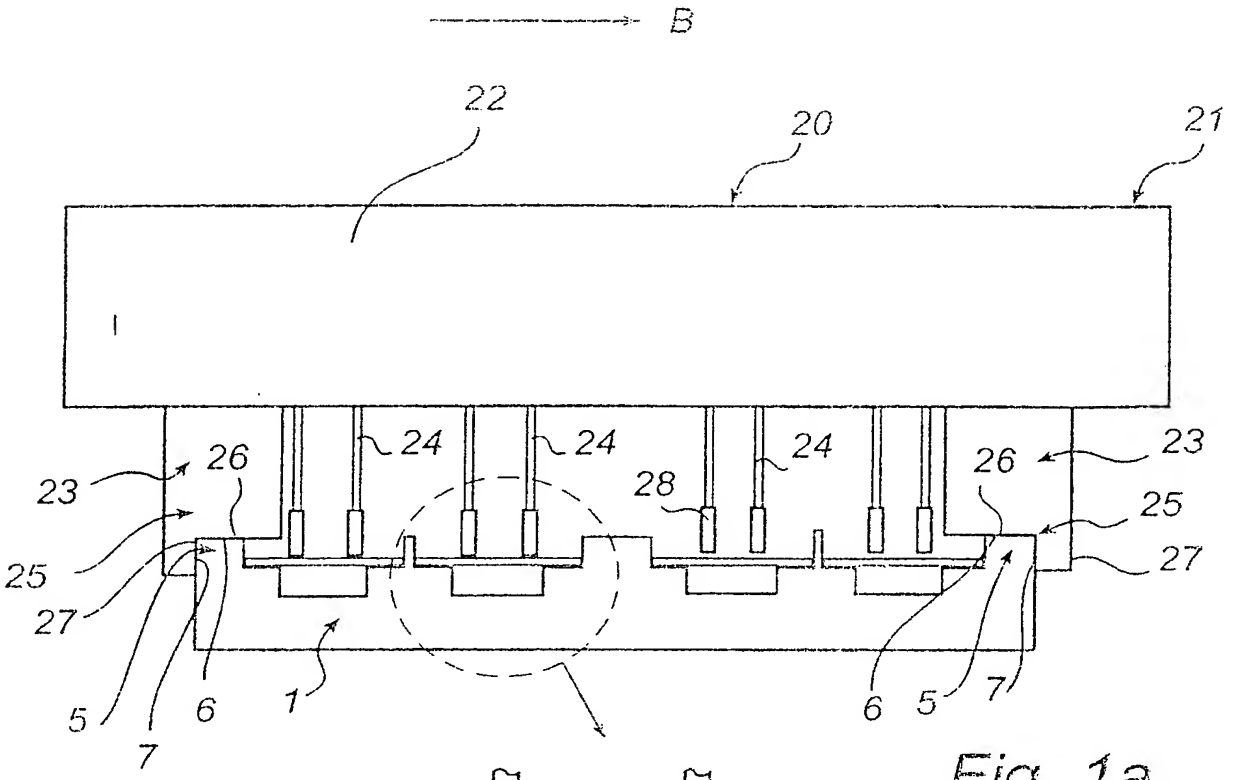
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Fig. 1a

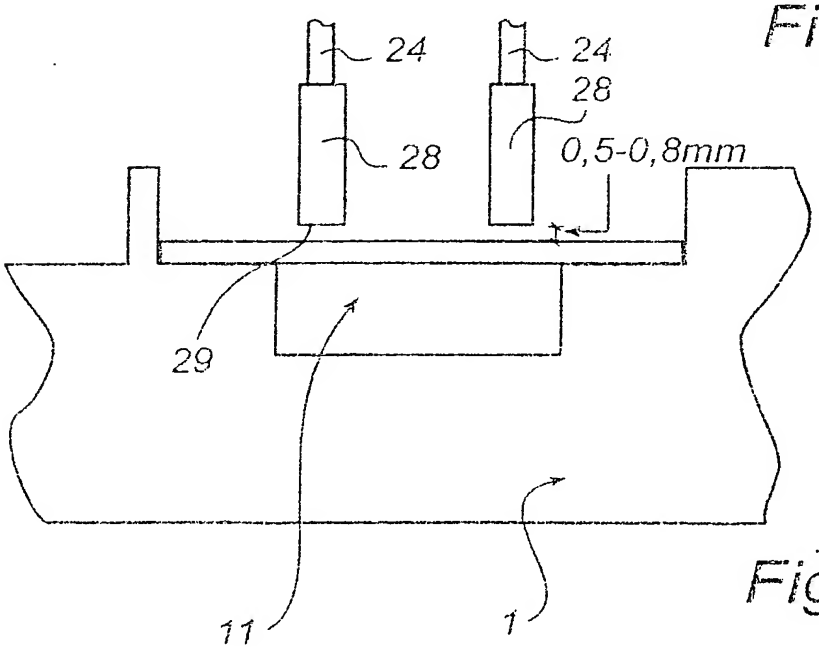
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Fig. 1b

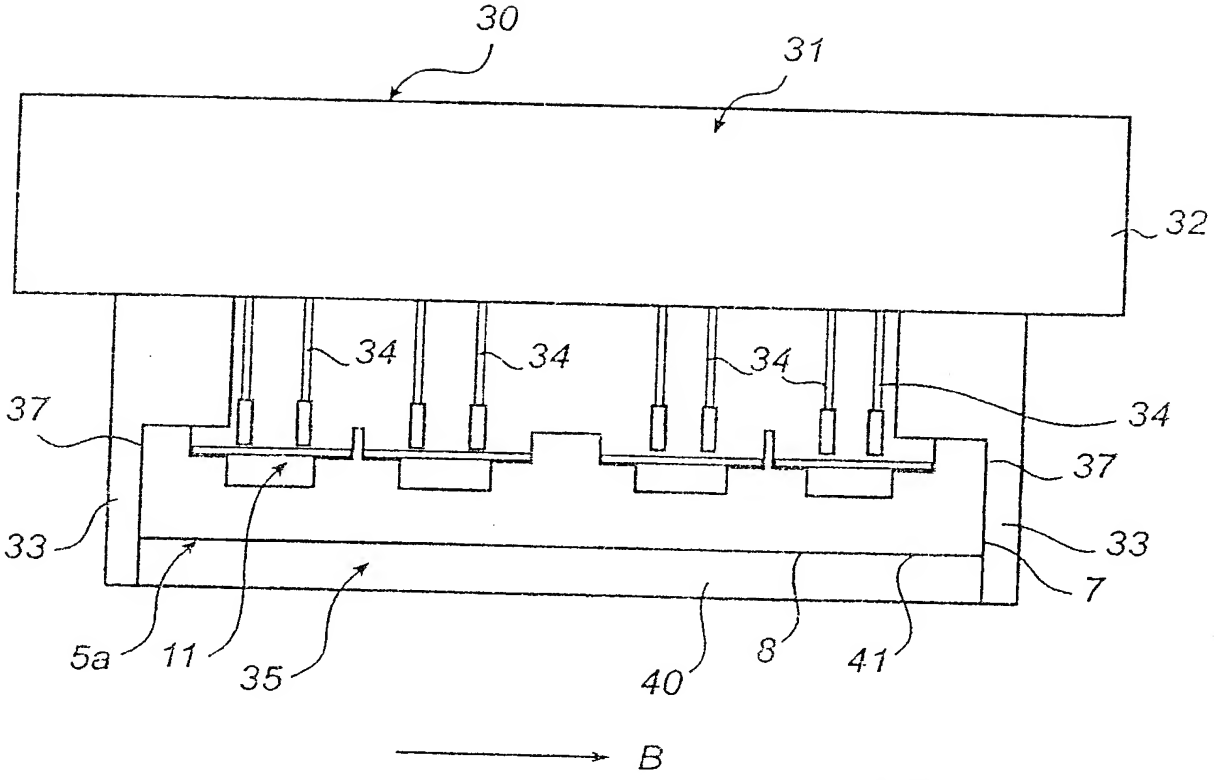

Fig. 2

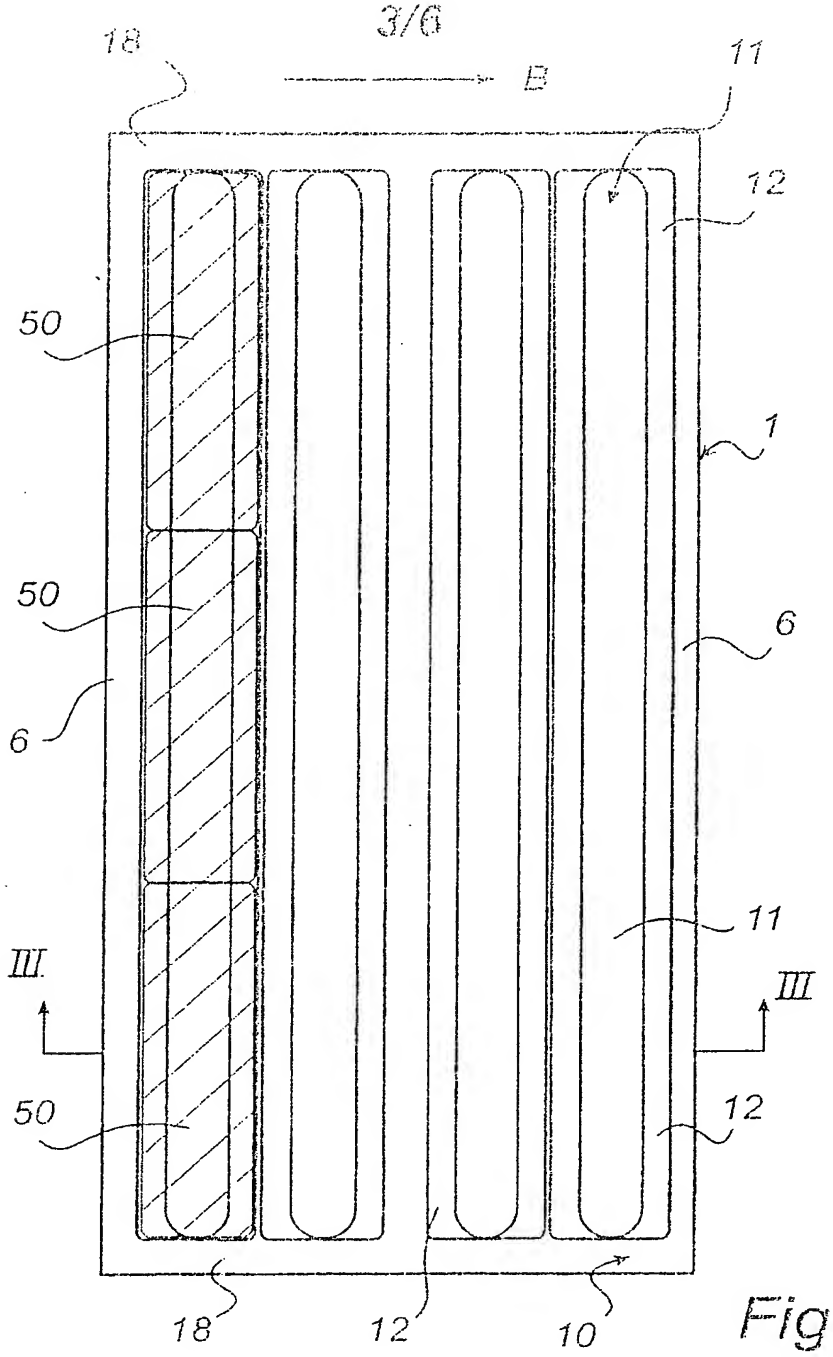
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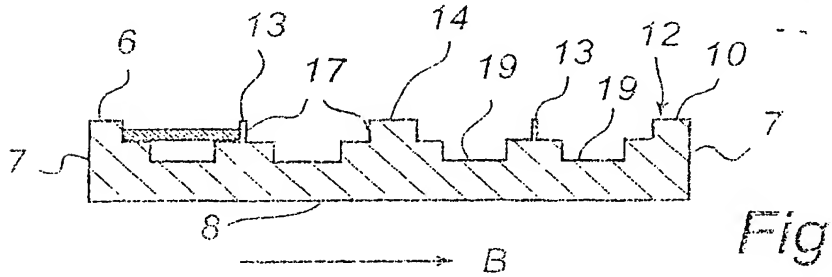
Fig. 3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7
7
8
B

Fig. 4

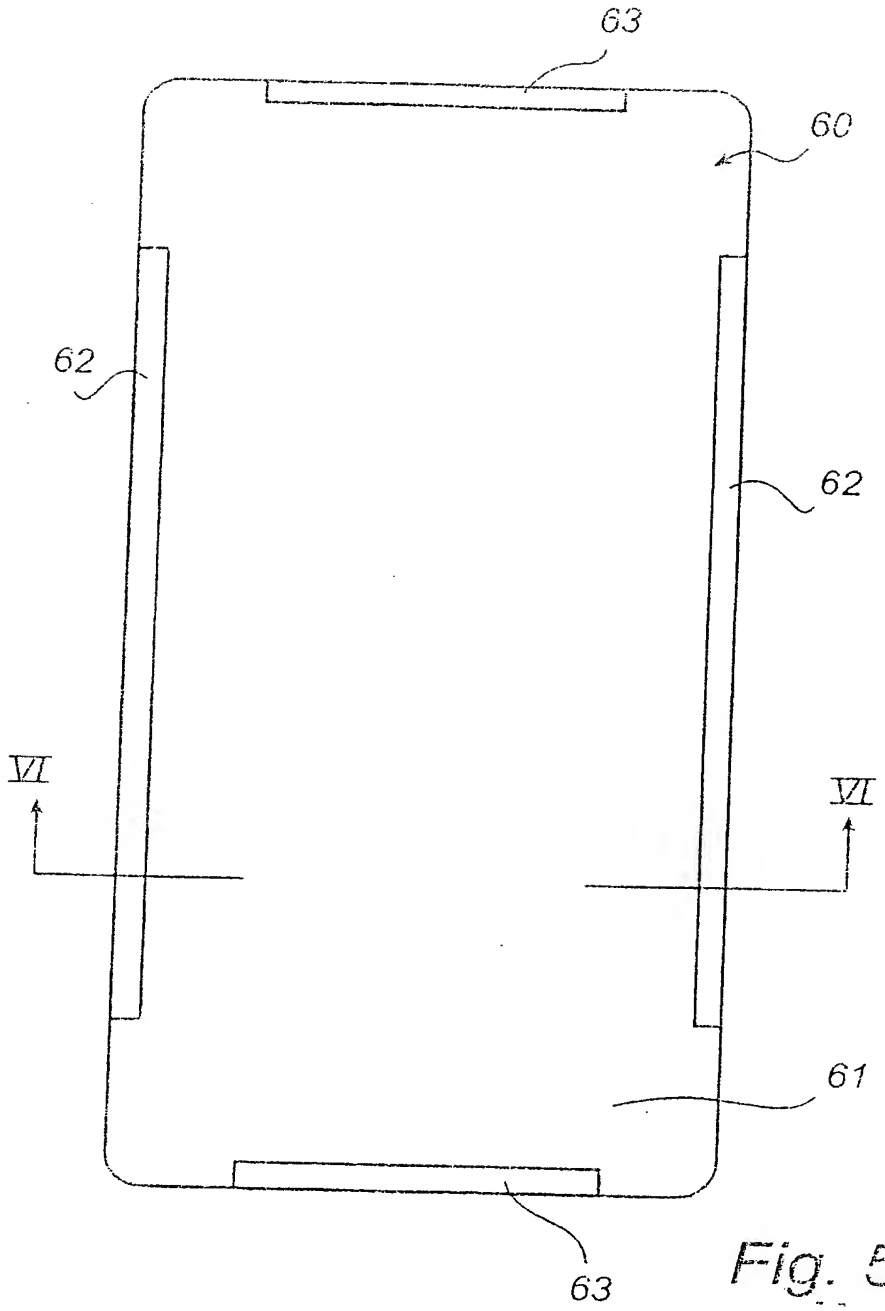

Fig. 5

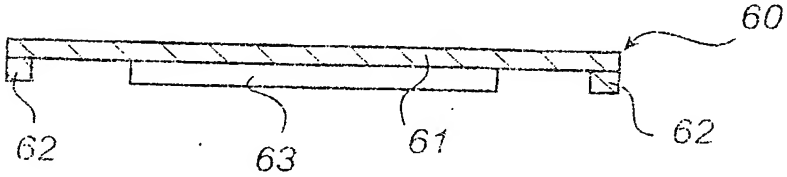

Fig. 6

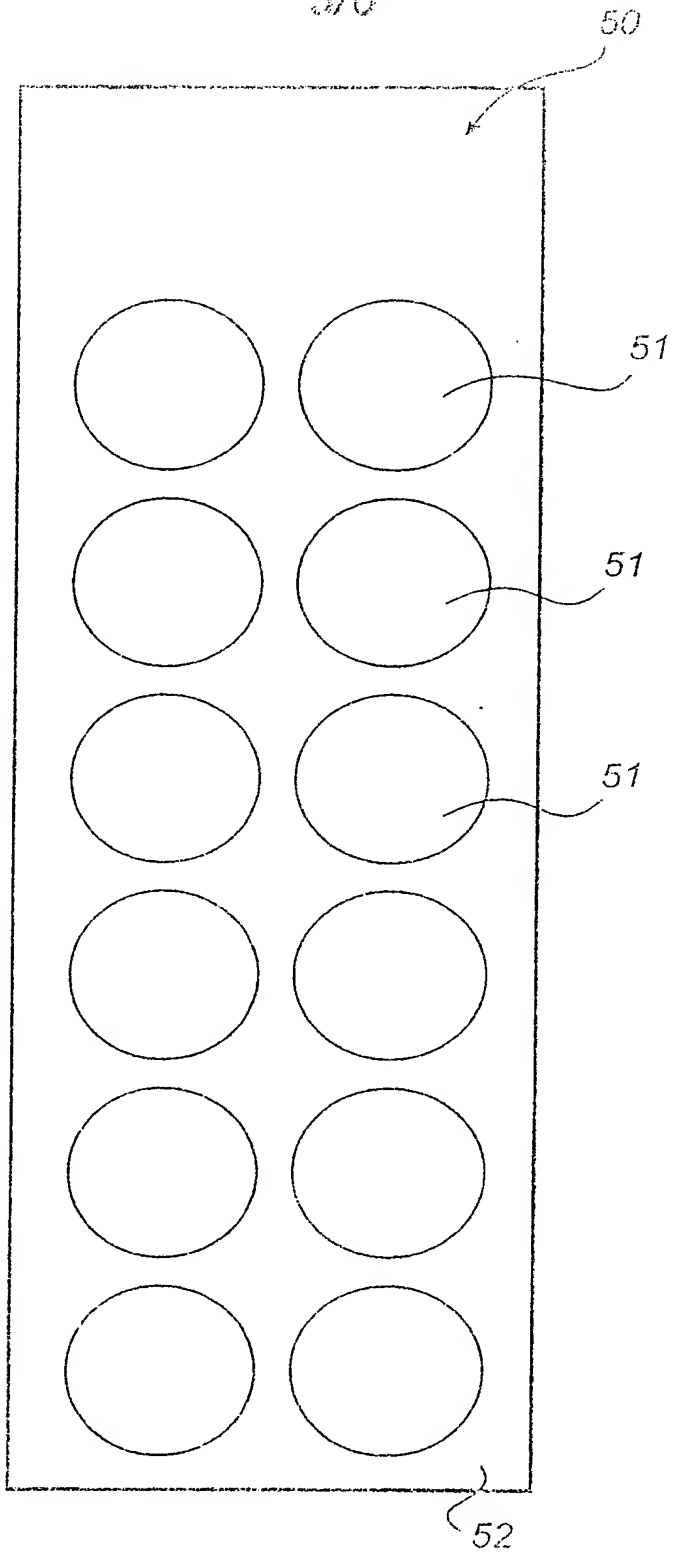

Fig. 7

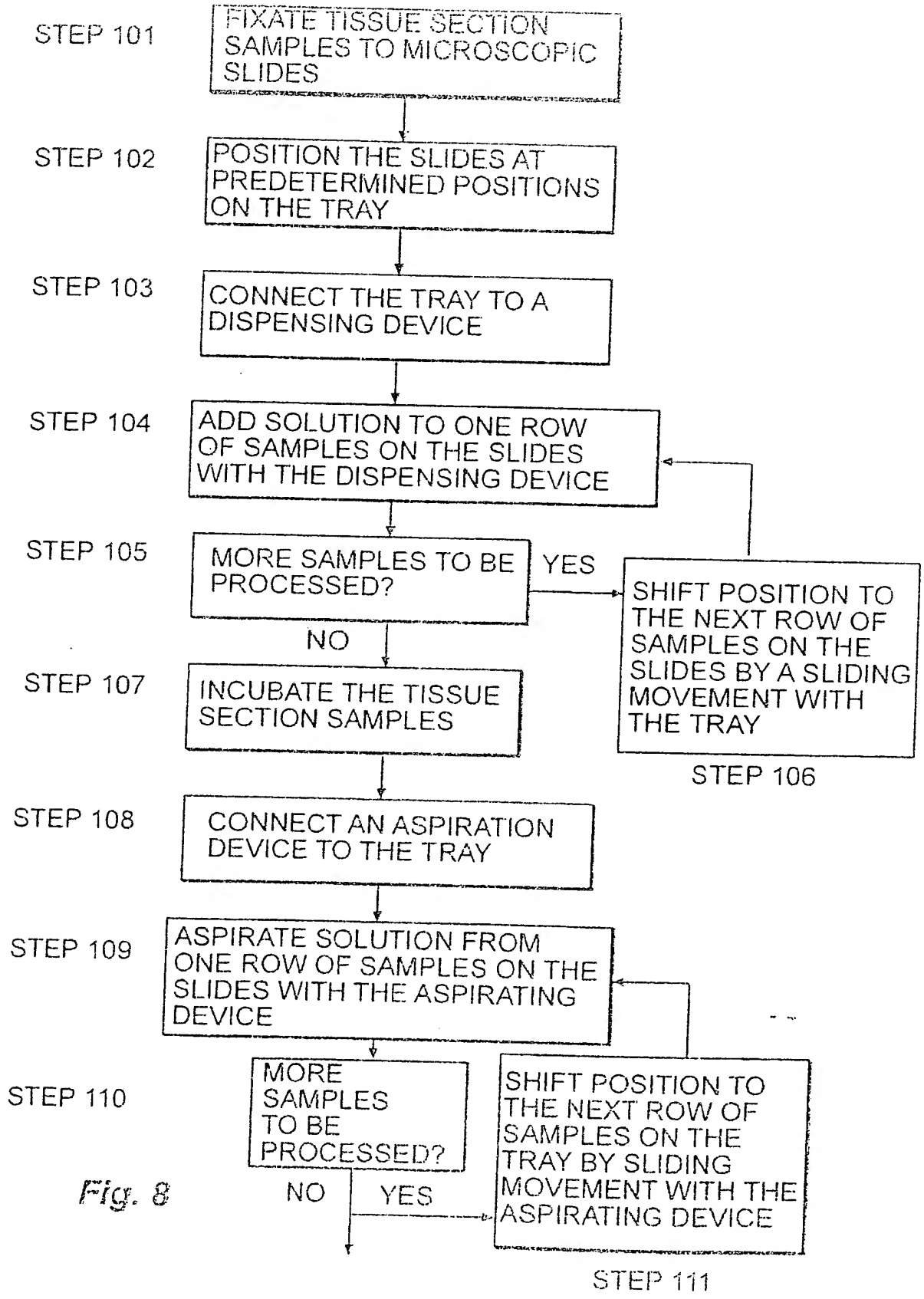
STEP 101
FIXATE TISSUE SECTION SAMPLES TO MICROSCOPIC SLIDES
STEP 102
POSITION THE SLIDES AT PREDETERMINED POSITIONS ON THE TRAY
STEP 103
CONNECT THE TRAY TO A DISPENSING DEVICE
STEP 104
ADD SOLUTION TO ONE ROW OF SAMPLES ON THE SLIDES WITH THE DISPENSING DEVICE
STEP 105
MORE SAMPLES TO BE PROCESSED?
YES
NO
SHIFT POSITION TO THE NEXT ROW OF SAMPLES ON THE SLIDES BY A SLIDING MOVEMENT WITH THE TRAY
STEP 106
STEP 107
INCUBATE THE TISSUE SECTION SAMPLES
STEP 108
CONNECT AN ASPIRATION DEVICE TO THE TRAY
STEP 109
ASPIRATE SOLUTION FROM ONE ROW OF SAMPLES ON THE SLIDES WITH THE ASPIRATING DEVICE
STEP 110
MORE SAMPLES TO BE PROCESSED?
NO
YES
SHIFT POSITION TO THE NEXT ROW OF SAMPLES ON THE TRAY BY SLIDING MOVEMENT WITH THE ASPIRATING DEVICE
STEP 111

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02359

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 1/30, G01N 1/31
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9944031 A1 (CYTOLOGIX CORPORATION), 2 Sept 1999 (02.09.99), page 10, line 24 - page 12, line 8 --	1,8,9
Y	US 4274359 A (JOSEPH P. DI MAGGIO, JR. ET AL), 23 June 1981 (23.06.81), column 3, line 17 - column 4, line 55 --	1,8,9
A	US 5338358 A (YOSHITADA MIZUSAWA ET AL), 16 August 1994 (16.08.94), column 3, line 32 - column 4, line 30 --	1-13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2001	08-03-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Ulla Granlund/MP Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02359

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0255057 A2 (HOECHST AKTIENGESELLSCHAFT), 3 February 1988 (03.02.88), column 2, line 15 - line 29 ---	1-13
A	US 4046927 A (JOHN MELNYK), 6 Sept 1977 (06.09.77), column 1, line 65 - column 2, line 64 --- --------	1-13

INTERNATIONAL SEARCH REPORT
Information on patent family members

05/02/01

International application No.
PCT/SE 00/02359

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NO 172413 B,C	05/04/93
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US 4046927 A	06/09/77	NONE	

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